LOW LEVEL VIRAEMIA

17TH AWACC 2025

30 OCTOBER

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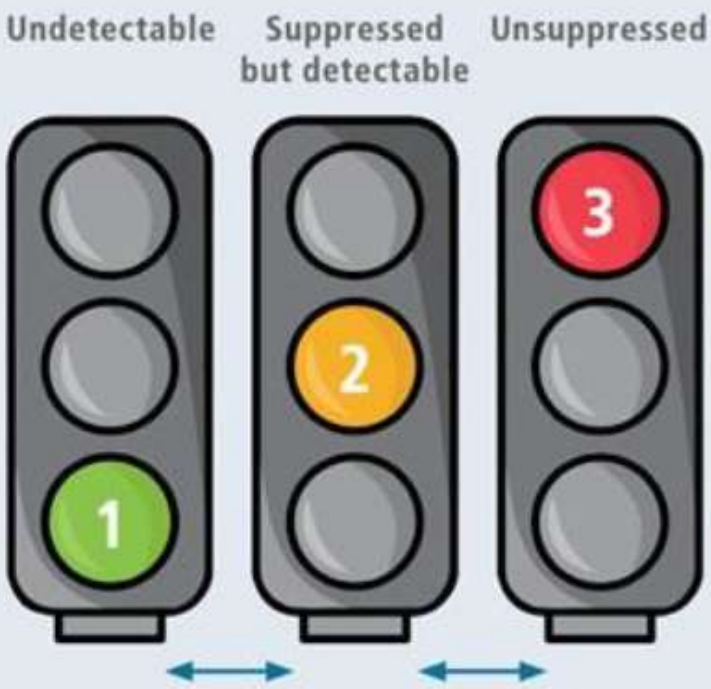


1 **Undetectable (not detected*)**: no measurable virus. Zero risk of transmission to sexual partner(s); minimal risk of transmission to children.

2 **Suppressed (detected but ≤1000 copies/mL)**: some virus replicating and present: could be due to missing doses, recent treatment initiation or drug resistance. Almost zero risk of transmission to sexual partner(s).

3 **Unsuppressed (>1000 copies/mL)**: significant virus replicating and present: could be due to missing doses, recent treatment initiation or drug resistance. Increased risk of falling ill and/or passing virus on to sexual partner(s) or children.

HIV LOW LEVEL VIRAEMIA

DEFINITIONS & OCCURRENCE

Persistent presence of HIV in the bloodstream between 50 and 1000 copies/ml while on ART -a state where the virus is detectable but typically below the level considered as virological failure

VF &DR ,MORTALITY

Associated with increased risk of virological failure

and mortality

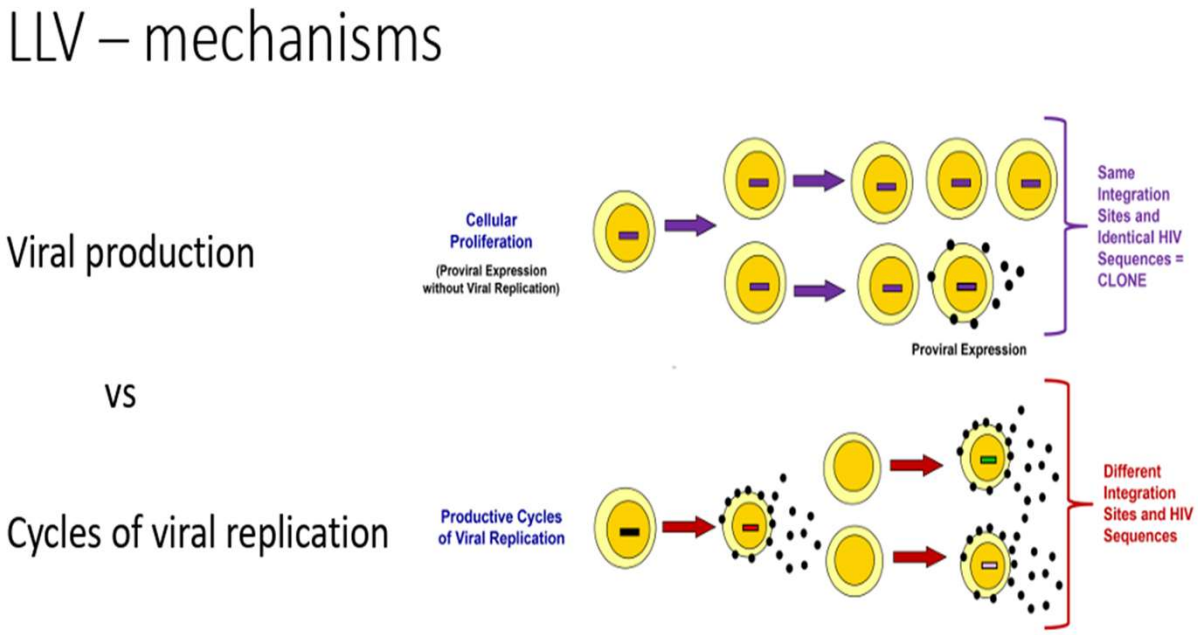
May be associated with significant levels of HIV drug resistance

MANAGEMENT

There are some good guidelines for clinical management and others are still bring researched

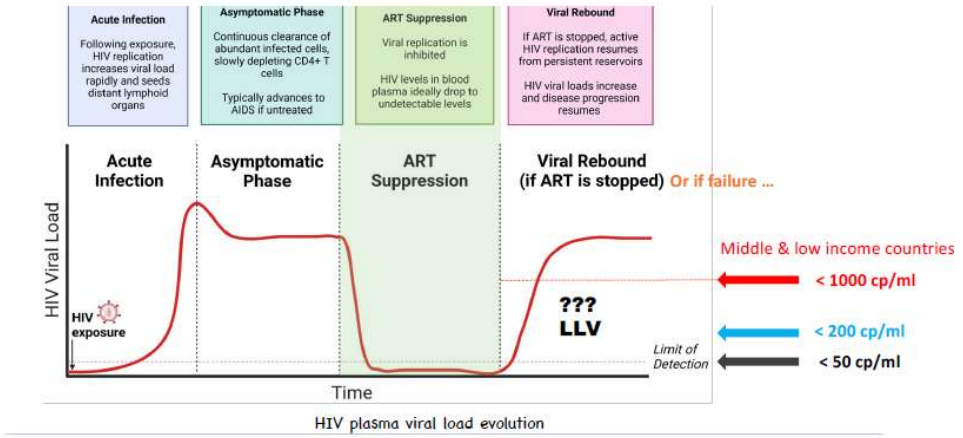
Potential causes of LLV …

- Incomplete suppression of HIV VL replication
- Release of HIV from latent reservoirs
- Adherence factors



obs et al, Front Microbiol, 2019

Suppression vs viral load threshold



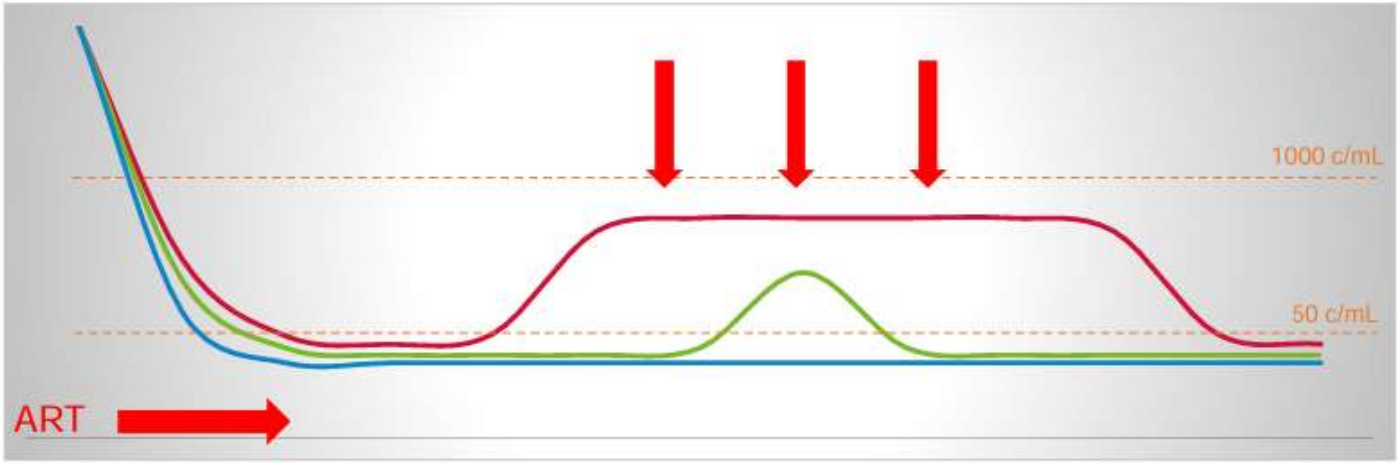
HIV plasma viral load evolution

LLV - National and regional guidelines

- Recommendations have changed over the past years
- Additional considerations on management of LLV have been added
- Thresholds for failure have not yet been adjusted (except SAHIVSOC)

Guidelines	WHO (2021)	SA HIV Clin Soc (2020)	SA DoH (2019)	Botswana MoH (2016)
Virological suppression	50 c/mL	50 c/mL	50 c/mL	50 c/mL
Virological failure	1000 c/mL	50 c/mL	1000 c/mL	400 c/mL

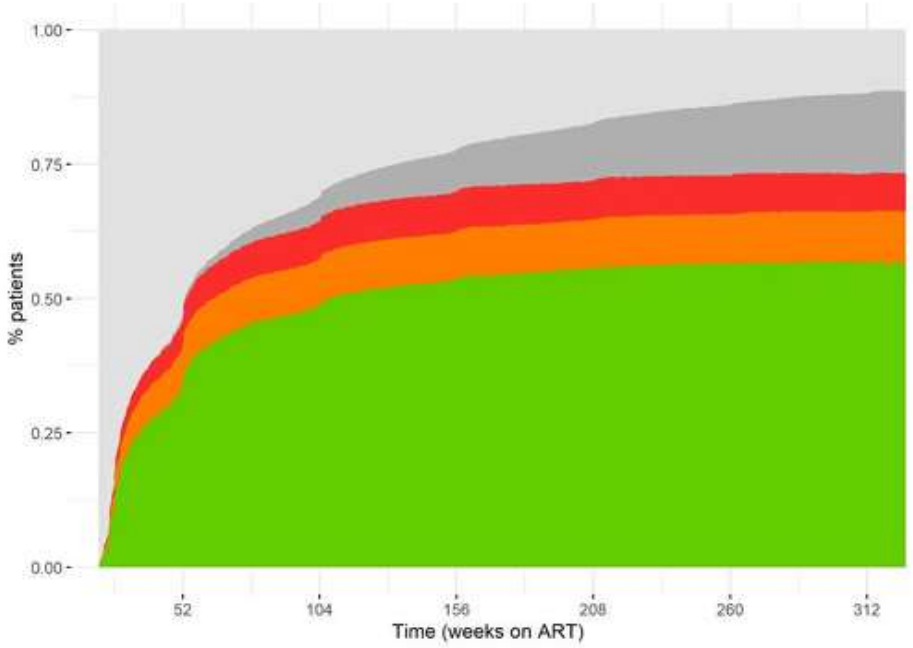
LLV - classification



- **Transient LLV ("blip")**: 1 LLV measurement preceded and followed by suppression within several months
- **Persistent LLV**: at least 2 consecutive LLV measurements

→ Classification requires high frequency VL monitoring…

LLV - a common occurrence



← Loss to follow-up

← VL ≥1000 copies/mL

← LLV 50-999 copies/mL

← Suppression <50 copies/mL

Approximately 10% at any point in time have LLV

- N = 102064 adult patients on first-line (>98% TEE)
- 52 clinics in South Africa (GP, LP, MP, NW)
- 2007-2018: 6 year follow-up visualised

Hermans et al, Plos Med, 2020

Low level Viraemia –KZN over 12 months Sept 2023

> 15 year age

VF (<1000) = 93807 (93.3)

VL > 1000 = 6.7 %.

VL<50 = 80.5%

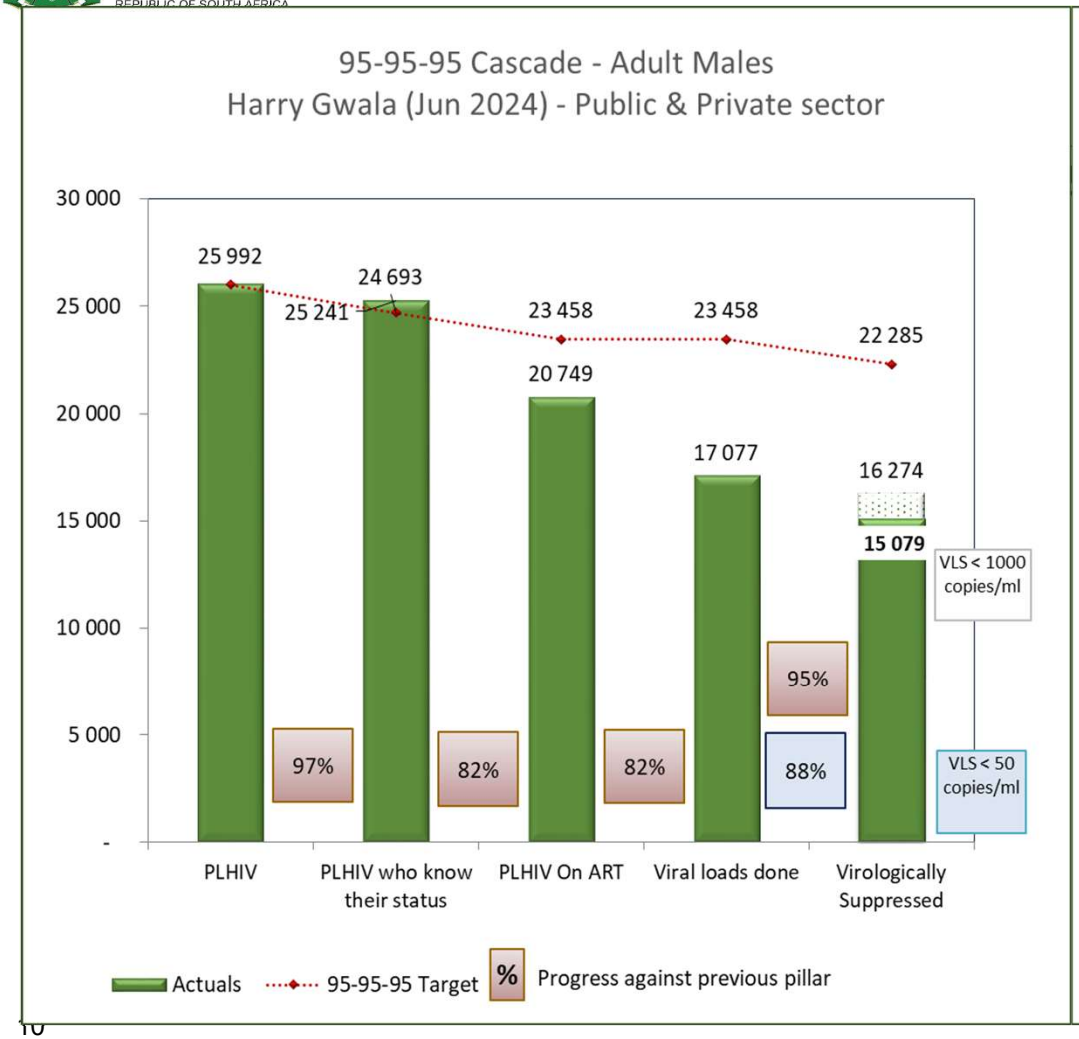
LLV (50-999) = 200 721 (13.2%)

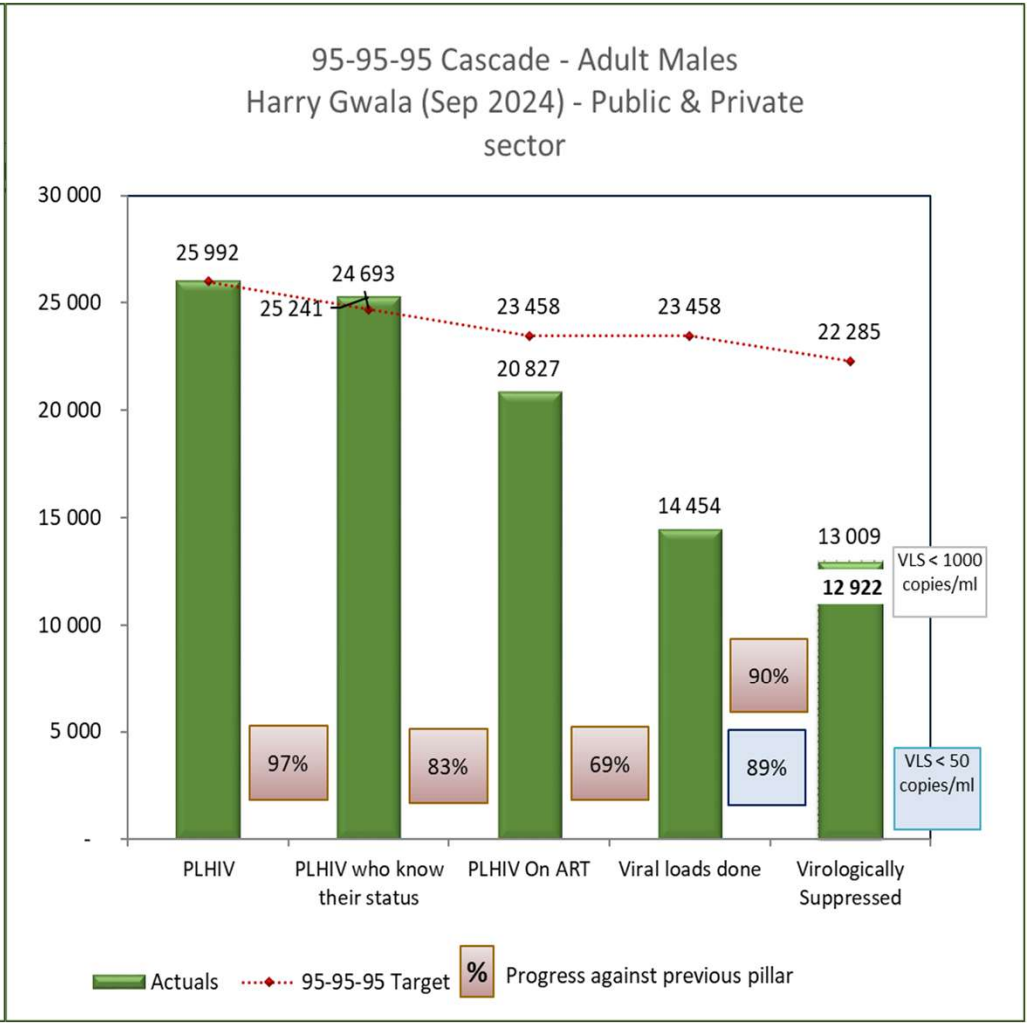
KZN: <15 YEARS AGE

- VL<1000: 73.6 %
- VL<50 -53.2
- 50-999 = 799 (29.7%)

KZN: 15-19 YEARS AGE

- VL1000: 78%
- VL 50: 60.4%
- 50-999 = 736 (22.59)


95-95-95 Cascade - Adult Males
Harry Gwala (Jun 2024) - Public & Private sector
30 000
25 000
20 000
15 000
10 000
5 000
-
25 992
25 241
24 693
23 458
23 458
22 285
20 749
17 077
16 274
15 079
97%
82%
82%
95%
88%
VLS < 1000 copies/ml
VLS < 50 copies/ml
PLHIV
PLHIV who know their status
PLHIV On ART
Viral loads done
Virologically Suppressed
Actuals
95-95-95 Target
%
Progress against previous pillar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13 009
12 922
97%
83%
69%
90%
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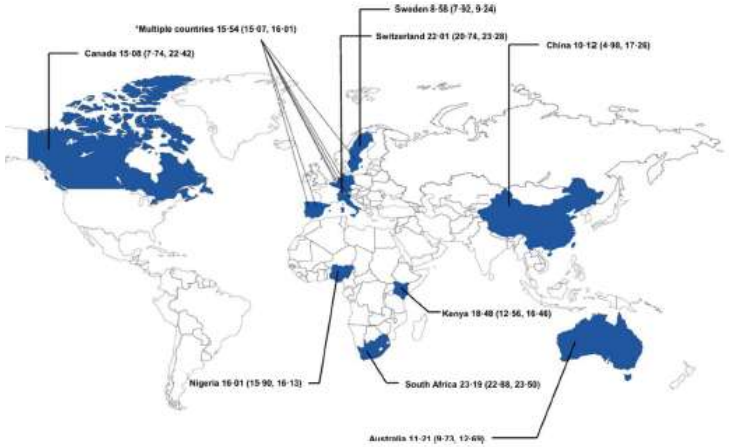
Emerging Microbes & Infections
2025, VOL. 14, 2447613 (11 pages)
https://doi.org/10.1080/22221751.2024.2447613

The prevalence of low-level viraemia and its association with virological failure in people living with HIV: a systematic review and meta-analysis

Shengnan Zhao [a], Wenjing Wang [a], Sibo Li [a], Jiaze He [a], Wenshan Duan [a], Zhen Fang [a], Xiaoran Ma [b], Zhen Li [c], Caiping Guo [a], Wen Wang [a], Hao Wu [a], Tong Zhang [a] and Xiaojie Huang [a]



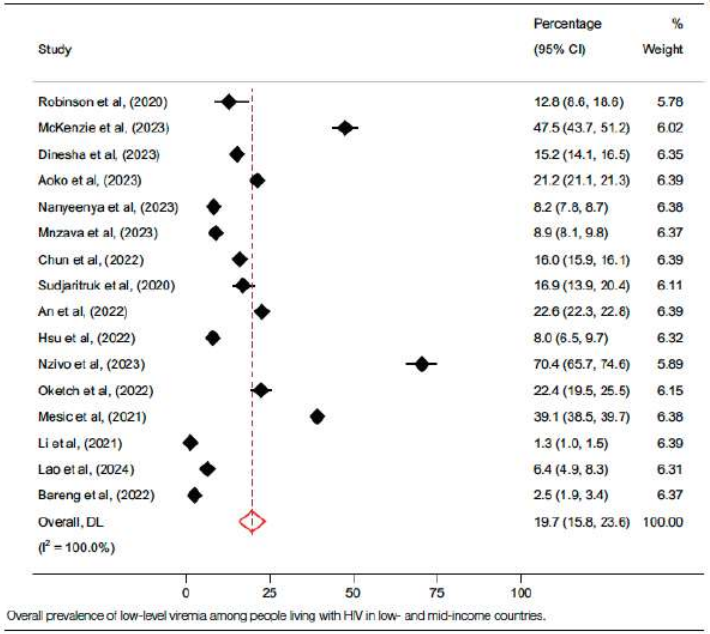
- **16 cohort studies**
- **1349306 PLHIV**
- **13.81% pooled prevalence of LLV**

LLV increased the risk of VL in 2.77%
And the risk of mortality at high VL in 1.66%

Systematic Review/Meta-Analysis
ANNALS OF MEDICINE & SURGERY
OPEN

Impact of low-level viremia on HIV non-viral load suppression in low and middle-income countries

Mbishi et al., (2025)



Overall prevalence of low-level viremia among people living with HIV in low- and mid-income countries.

- **1 159 317** PLHIV were analyzed.
- Pooled prevalence of LLV was **19.7%**

% of LLV was significantly higher among children compared to adults (**25.8%** vs **17.2%**; P < 0.001)

Overall, LLV increased the risk of non-VLS on a subsequent VL test compared to fully suppressed (RR = 2.6; 95% CI: 2.2–3.1).

J Antimicrob Chemother 2022; **77**: 1385–1395
https://doi.org/10.1093/jac/dkac056 Advance Access publication 1 March 2022

Journal of Antimicrobial Chemotherapy

HIV-1 drug resistance mutations among individuals with low-level viraemia while taking combination ART in Botswana

Bareng et al., JAC 2022

Table 2. Prevalence of HIV DRMs stratified by VL group at enrolment

Resistance measure	Total $N=332$	LLV (51–999 copies/mL) $N=157$	VL ≥ 1000 copies/mL $N=175$	*P* value
Any mutation, *n* (%)	135 (41) 95% CI: 35–46	57 (36) 95% CI: 29–44	78 (45) 95% CI: 37–52	0.09
Resistance category, *n* (%)				
NRTI-associated	55 (17)	17 (11)	38 (22)	0.007
NNRTI-associated	116 (35)	50 (32)	66 (38)	0.18
PI-associated	19 (6)	7 (4)	12 (7)	0.23
INSTI-associated	10 (3)	6 (4)	4 (2)	0.28
		36% HIVDR <1000 copies/ml	45% HIVDR >1000 copies/ml	

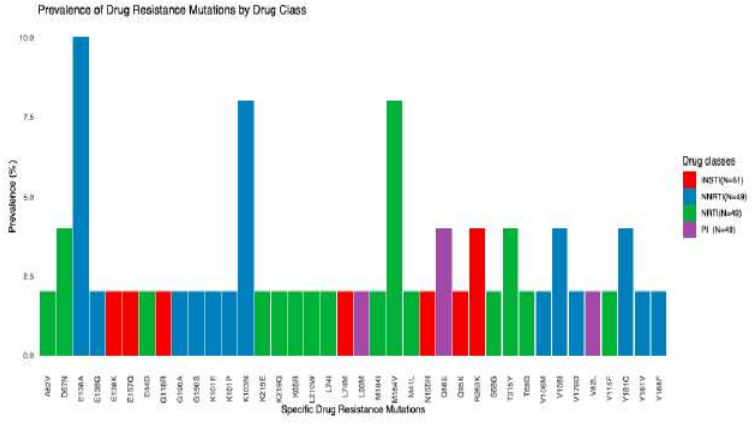
The OR of experiencing VF in persons with LLV at entry was **36-fold higher** than in the virally suppressed group

J Antimicrob Chemother 2025; **80**: 767–776
https://doi.org/10.1093/jac/dkae472 Advance Access publication 7 January 2025

Journal of Antimicrobial Chemotherapy 50 years

High prevalence of reverse transcriptase inhibitors associated resistance mutations among people living with HIV on dolutegravir-based antiretroviral therapy in Francistown, Botswana

Choga et al., JAC 2025



LLV – increased risk of mortality

- Swedish InfCare HIV Cohort (1996-2017)
  - N = 6956 adult PLHIV

- LLV was associated with:
  - ↑ all-cause mortality
  - ↑ serious non-AIDS events
  - But not associated with AIDS events

→ Is LLV a signal of risk behavior?

	Fully Adjusted Model[a]
All-cause mortality, n	4541
Virologic suppression	1 (Ref)
LLV of 50–199 copies/mL	2.2 (1.3–3.8)
LLV of 200–999 copies/mL	2.1 (.96–4.7)
Nonsuppressed viremia	7.7 (3.7–15.8)
Serious non-AIDS events, n	4486
Virologic suppression	1 (Ref)
LLV of 50–199 copies/mL	.86 (.50–1.5)
LLV of 200–999 copies/mL	2.0 (1.2–3.6)
Nonsuppressed viremia	3.3 (1.8–6.0)

Elvstam et al, CID, 2021

Persistent LLV (PLLV) and high LLV (PHLLV) correlate with increased risks of non-AIDS conditions such as cancers, cardiovascular events, liver cirrhosis, and kidney disease, alongside chronic immune activation and inflammation.

Ganesan A et al. *Low-level viremia is associated with serious non-AIDS events in people with HIV*. Open Forum Infectious Diseases, published online 30 March 2024.

LLV and CNS escape

- LLV during ART may be associated with discordant (high) CSF HIV-1 RNA levels[1]
- CSF virus often harbours resistance mutations[1,2,3,4]
- Some patients may be neurosymptomatic[2]

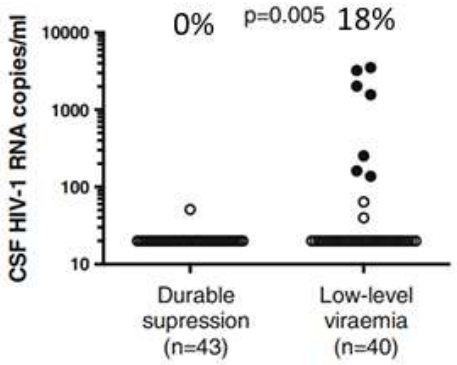


Table 2. Drug resistance mutations in CSF.

PID	VL (copies/ml) PI/CSF	Drug resistance mutation
0161	<40/1350	None detected
0213	<40/1330	V82A/D67N/K70E/L74I/V106M/M184V/G190A
0189	12802/310	K65R/V75I/M184V/L100I/K103N/P225H
0133	19551/28250	M46I/V82A/D67N/K70R/M184V/T215F/K103N/K238T
0183	58000/1300	D67N/M184V/K103N/V106M
0140	254/21370	K101E
0164	620/2900	K101E
0168	936/3030	None detected
0172	24000/801	None detected

1: Nightingale et al, J Neurovirol, 2016
2: Mukerji et al, JAIDS, 2017
3: Lustig et al, Plos Pathogens, 2021
4: Lelyveld et al, CID, 2010

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Management of low-level HIV viremia during antiretroviral therapy: Delphi consensus statement and appraisal of the evidence-2024

Rindi LV, Zaçe D, Compagno M, Colagrossi L, Santoro MM, Andreoni M, Perno CF, Sarmati L; Low-level HIV Viremia Consensus Panel. Management of low-level HIV viremia during antiretroviral therapy: Delphi consensus statement 2024-056199. PMID: 39288982; PMCID: PMC11503133.

Results Overall,

18/32 statements (56.2%) achieved a strong consensus, 3/32 (9.4%) achieved a moderate consensus and 11/32 (34.4%) did not achieve a consensus.

Key findings include

- Recommendations on ART regimen modification
- Genotypic resistance testing,
- Adherence assessment,
- Therapeutic drug monitoring and
- Follow-up strategies.

Strategies indicated in selected circumstances included

Quantifying total HIV-1 DNA and

Evaluating concomitant chronic infections.

Conclusions

Acknowledging the many uncertainties about source, significance and optimal management of low-level viremia during ART, Findings provide insights to help harmonise clinical practice.

Need for well-designed randomised studies assessing different interventions to manage low-level viremia and future research regarding its definition

Research Gaps: There is a scarcity of robust studies and clear guidelines on managing PLLV and PVLLV despite their prevalence (18%-34%) and associated risks, highlighting the need for further research and updated clinical recommendations.

How do we measure adherence?

More Objective Measures

Automatic compilation of dosing history data

Electronic monitoring

Sensor devices (ingested)

Pharmacologic measures

Pharmacy refill data

Retrospective questionnaire

Pill Counts

Patient diaries

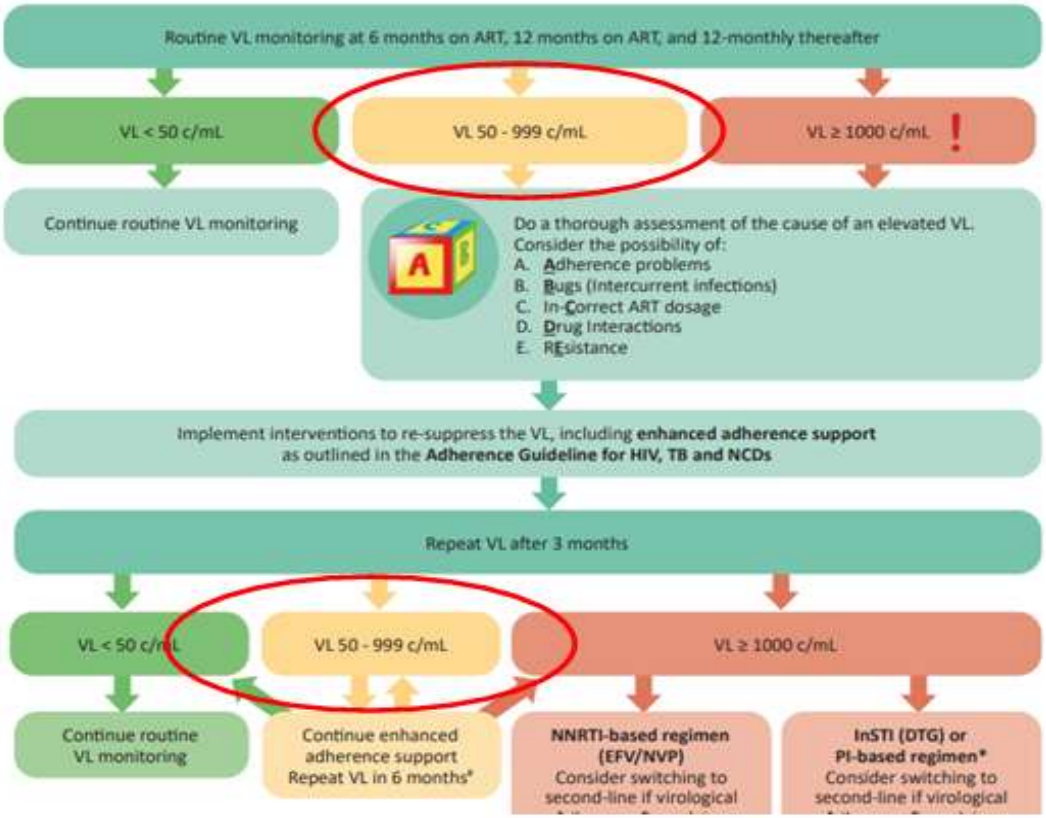
Self-report

More Subjective Measures

Modified from Vrijens & Urquhart, 2005 Journal of Antimicrobial Chemotherapy.

LLV – SA DoH recommendations

- Example: SA DoH



Take home message

- LLV is associated with virological failure , drug resistance , and clinical issues
- Should we keep staying at 1000 copies/ml with the current effective ART like INSTIs?
- Importance of VL monitoring because need to monitor adherence or the potential for drug resistance
- More research is needed to understand the causes and optimal management of LLV

Acknowlegements …

Dr Avelin AGHOKENG –IRD

2. Dr Lucas Hermans – UCT /ITREMA RESEARCH GROUP

3. Dr .Richard Lessells –AHRI ,UKZN

4. Suzanne McCluskey, Massachusetts General Hospital ,Harvard

THANK YOU

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